Management of Volume Overload in the Hospitalized Patient with Heart Failure - the Science and the Art

Uri Elkayam, MD

LAHeartFailure.com
Management of Volume Overload in Patients with Heart Failure: The Science and the Art

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In 2014, there were about 1 million hospitalizations with acute HF in the US. 

National Burden of Heart Failure Events in the United States, 2006 to 2014

Nationwide Emergency Department Sample

Jackson SL. Circ Heart Fail. 2018;11:e004873
The use of diuretics in heart failure with congestion

- The vast majority of patients with AHF present with symptoms and signs of congestion with volume and pressure overload.
- The goal of therapy is the relief of congestion and achieving euvolemia and hemodynamic and symptomatic improvement.

A position statement from the Heart Failure Association of the ESC
European Journal of Heart Failure (2019) 21, 137–155
Many Patients Have Little or No Weight Loss During Hospitalization

Volume Overload - Treatment

Diuretics
Ultrafiltration
Renal dose dopamine.
Vasopressin antagonists.
Patients with volume overload should be treated with IV loop diuretics (1, B).

How should we use diuretics in patients with AHF?
Diuretic Strategies in Patients with Acute Decompensated Heart Failure

High dose vs. low dose
Bolus administration vs. continuous infusion
DOSE Trial - Design

- **Low IV dose:**
  Total daily oral dose.
  (80mg=80mg)

- **High IV dose:**
  2.5 X total daily oral dose
  (80mg=200mg)
# Low vs. High Dose

## Results over 72 hours

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Low dose N=151</th>
<th>High dose N=157</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC for dyspnea</td>
<td>4478±1550</td>
<td>4668±1496</td>
<td>0.04</td>
</tr>
<tr>
<td>Change in weight (Lb.)</td>
<td>-6.1±9.5</td>
<td>-8.7±8.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Net fluid loss (ml)</td>
<td>3575±2635</td>
<td>4899±3479</td>
<td>0.001</td>
</tr>
<tr>
<td>Chang in NTproBNP (pg/ml)</td>
<td>-1194±4094</td>
<td>-1882±4105</td>
<td>0.06</td>
</tr>
</tbody>
</table>
## Bolus vs. Continuous

### Results over 72 hours

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Bolus</th>
<th>Continuous</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=156</td>
<td>N=152</td>
<td></td>
</tr>
<tr>
<td>AUC for dyspnea</td>
<td>4456±1448</td>
<td>4699±1573</td>
<td>0.36</td>
</tr>
<tr>
<td>Change in weight (Lb.)</td>
<td>-6.8±7.8</td>
<td>-8.1±10.3</td>
<td>0.20</td>
</tr>
<tr>
<td>Net fluid loss (ml)</td>
<td>4237±3208</td>
<td>4249±3104</td>
<td>0.89</td>
</tr>
<tr>
<td>Chang in NTproBNP (pg/ml)</td>
<td>-1316±4364</td>
<td>-1773±3828</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Higher bolus dose 200 mg/d vs 160 mg/d (p=0.06)
There was no bolus before the start of continues infusion
Stepped Pharmacologic Care Algorithm For ADHF

<table>
<thead>
<tr>
<th>Level</th>
<th>Current Daily Furosemide Dose a, mg</th>
<th>Bolus</th>
<th>Infusion Rate, mg/h</th>
<th>Metolazone (Oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤80</td>
<td>40</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>81–160</td>
<td>80</td>
<td>10</td>
<td>5 mg daily</td>
</tr>
<tr>
<td>3</td>
<td>161–240</td>
<td>80</td>
<td>20</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td>4</td>
<td>≥240</td>
<td>80</td>
<td>30</td>
<td>5 mg twice daily</td>
</tr>
</tbody>
</table>

a Diuretic equivalents: 40 mg furosemide is considered equivalent to 1 mg bumetanide 20 mg torsemide. Adapted from Grodin

Bart BA et al. CARESS Trial NEJM 2012;367:2296-2304
CARESS Trial
COMPARATIVE EFFECT ON URINE OUTPUT
Ng T, Elkayam U et al  J CV Pharm Therapy  2012

Mean difference b/w baseline and refractory regimen
-48±103*  -109±171*†  -90±90*†  *p<0.0001 vs baseline  †p<0.0087 between groups

N=160  N=42  N=40

Continuous infusion  furosemide
Furosemide + metolazone
Continuous infusion  Bumetanide

UO Baseline (mL/h)  UO on Tx (mL/h)
Give high dose of IV loop diuretics (IIa,B) or Add a second diuretic (e.g. Metolazone or Thiazide, IIa,B).
Sites and mode of action and effects on sodium reabsorption in the nephron of different diuretics.

European Journal of Heart Failure (2019) 21, 137–155
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## COMPARATIVE EFFECT ON URINE OUTPUT

Ng T, Elkayam U et al :J CV Pharmacol Therap  2012;17:373

<table>
<thead>
<tr>
<th></th>
<th>Continuous infusion</th>
<th>Metolazone</th>
<th>Bumetanide</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of hyponatremia</td>
<td>29%</td>
<td>43%</td>
<td>63%</td>
<td>0.011 **</td>
</tr>
<tr>
<td>Incidence of hypokalemia</td>
<td>27%</td>
<td>46%</td>
<td>29%</td>
<td>0.095</td>
</tr>
</tbody>
</table>
Diuretic Strategies for Loop Diuretic Resistance in Acute Heart Failure

1,188 ± 476 ml of urine in 12 h during high-dose loop diuretic therapy (IV furosemide: 612 ± 439 mg/day).

Cox ZL et al JACC Heart Failure 2020;8:157–68
## End points at 48 hours

<table>
<thead>
<tr>
<th></th>
<th>Metolazone</th>
<th>Tolvaptan</th>
<th>P value Tolvaptan vs Metolazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net input &amp; output (Liters)</td>
<td>-4.6</td>
<td>-6.43</td>
<td>0.168</td>
</tr>
<tr>
<td>Change in serum Na mEq/L</td>
<td>-1 +/-3</td>
<td>+4 +/-5</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in serum Cl mEq/L</td>
<td>-7 +/-4</td>
<td>+2 +/-3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Change in serum Bicarbonate mEq/L</td>
<td>5 +/-6</td>
<td>+2 +/-4</td>
<td>0.06</td>
</tr>
<tr>
<td>Change in Scr mEq/L</td>
<td>0.3 +/-0.3</td>
<td>+0.03 +/-0.3</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Does Low Dose Dopamine Have a Role?
The Science and the Art

The ROSE Trial
Dopamine122 vs 61 placebo

Elkayam U et al
Circulation 2008;117:200-205

Figure 3. Percentage increase in RBF index (RBFI) and cardiac index (CI). The percentage increases in RBFI appeared to be greater than those of CI at different doses, reaching statistical significance at 5 μg · kg⁻¹ · min⁻¹.
A difficult HF patient with recurrent hospitalizations and cardiorenal syndrome. Admitted again with renal shutdown that did not respond to diuretics and was put on dialysis, I decided to give it a try and gave him dopamine with amazing response! He gave 1.5 liters on the first day (after giving less than 100ml daily before) and went up to 3 liters a day. He is now off dialysis and off Dopamine and everybody think that I’m a king so thank you for your teaching. Ofer Havakuk, MD
Increased Scr During Successful Treatment of Volume Overload

What is the Clinical significance?
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Low dose</th>
<th>High dose</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in Scr &gt; 0.3 mg/dL</td>
<td>14%</td>
<td>23%</td>
<td>0.04</td>
</tr>
<tr>
<td>Median length of stay (days)</td>
<td>6</td>
<td>5</td>
<td>0.42</td>
</tr>
<tr>
<td>Alive and out of the hospital (days)</td>
<td>50</td>
<td>52</td>
<td>0.42</td>
</tr>
</tbody>
</table>
Figure 3  Patients’ Global Assessment of Symptoms (VAS) During the 72-h Study Treatment Period and Changes in Serum Creatinine Over Time

(A) Patients’ global assessment of symptoms was quantified as the area under the curve (AUC) of serial assessments from baseline to 72 h. Mean (± SD) AUCs are shown for the group that received a low dose of the diuretic compared with the group that received a high dose. (B) The mean change in serum creatinine level over the course of the study is shown for the group that received a low dose of the diuretic compared with the group that received a high dose. VAS = visual analog scale. Reprinted, with permission, from Felker et al. (18).
**Figure 1.** Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response).
CARRESS – HF

Figure 2. Changes from Baseline in Serum Creatinine and Body Weight at Various Time Points, According to Treatment Group. The P values were calculated with the use of a Wilcoxon test. The data on creatinine levels reflect results from testing in local laboratories only.
CARRESS - HF

Mortality

P = 0.465

Mortality and HF hospitalization

P = 0.956
31% of 903 patients with ADHF developed ≥20% increased GFR (IRF).

IRF was associated with greater incidence of post discharge WRF and increased mortality (HR 1.3, p=0.011)
Investigation of association between changes in Scr and 60 d mortality or rehospitalizations.

301 patients in the DOSE trial.

WRF = $>0.3 \text{ mg/dL}$ increase, IRF = $>0.3 \text{ mg/dL}$ decrease in Scr.

Increasing Scr was associated with lower risk (HR = 0.81, $P = 0.026$).

Decreasing Scr was associated with higher risk (HR = 2.52, $P < 0.001$).
Does Increased Scr really means worsening in renal function?
WRF in Patients with AHF Undergoing aggressive Diuresis is not associated with Tubular Injury

- 283 patients in the ROSE AHF trial.
- WRF = \( \geq 20\% \) decrease in GFR.
- Well validated tubular injury biomarkers N-acetyl-beta-d-glucoseaminidase, neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule 1 were measured.

Ahmad T et al
Circulation 2018;137:2016-28
WRF in Patients with AHF Undergoing aggressive Diuresis is not associated with Tubular Injury

- WRF occurred in 21% of the patients.
- There was no increase in the level of any of the markers of tubular injury in these patients.
- Conclusion: Increase in Scr during diuresis does necessarily mean WRF.
Is WRF an ominous prognostic sign in inpatients with ADHF?

Metra M et al Circ Heart Fail 2012;5:54

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariable HR</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ SCr + CONGESTION</td>
<td>2.44</td>
<td>0.0097</td>
</tr>
<tr>
<td>- sCr + CONGESTION</td>
<td>1.35</td>
<td>0.53</td>
</tr>
<tr>
<td>+ Scr – CONGESTION</td>
<td>1.04</td>
<td>0.88</td>
</tr>
<tr>
<td>- Scr – CONGESTION</td>
<td></td>
<td>Ref</td>
</tr>
</tbody>
</table>

N=599
Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure.

Relation between clinical evidence of congestion at 4 to 6 weeks and survival over subsequent 2 years for 146 patients hospitalized with NYHA class IV symptoms of chronic heart failure.

orthopnea, JVD, edema, weight gain, and new increase in baseline diuretics
Relation Between Residual Congestion and Outcome

Logeart D et al JACC 2004;43:635-41
Changes in serum creatinine during the treatment of ADHF should be evaluated in the context of the overall clinical status.

Keeping in mind that decongestion is the primary goal of treatment.
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